Claim Objections

Claim 5 is objected to for reciting the abbreviation "EGFR". Claim 5 has been amended to recite "epidermal growth-factor receptor (EGFR)".

Claim Rejections - 35 U.S.C. § 112, first paragraph

Claims 1-19 are rejected as not enabled. The Office Action states in particular that the specification is not enabling for the methods of the claimed invention or the organization of active agents such as a metalloprotease into pharmaceutically acceptable compositions or how to apply results from *in vitro* experiments into humans.

Applicants respectfully disagree. Applicants first point out that at the time of invention it was known that cancer or rather asthma are connected with increased expression and activation of growth-factor receptors and that low-molecular inhibitors or inhibitory antibodies are employed against these growth factor receptors in clinical studies.

The present invention is thus related to the fact that the processing of ligands of the EGF-family is regulated via G proteins and G-protein coupled receptors, wherein said regulation is mediated by means of metalloproteases, which in turn, leads to a regulation of the EGFR activity. This regulation of the EGFR activity has been shown in the present application for cancer cells. Therefore, according to the present invention, substances which inhibit G proteins, G-protein coupled receptors, metalloproteases or EGFR ligands, can also contribute to the inhibition of the EGFR receptor or receptors related thereto, and thus serve as a remedy against diseases associated with the enhanced activity or rather expression of these receptors.

One of skill in the art viewing the application would know how to formulate and use the pharmaceutical compositions and methods of the claimed invention. Applicants note that no evidence has been submitted which demonstrates any reason to doubt a reasonable correlation between the *in vitro* examples and *in vivo* activity for the claimed invention. Nor has any evidence been presented which indicates that those of skill in the art would be unable to determine dosage amounts from the disclosure of the application including the *in vitro* examples.

Because the initial burden is on the Examiner to give reasons for lack of enablement, the Examiner must also give reasons for a conclusion of lack of correlation between any *in vitro* examples and *in vivo* activity. All that is required is a reasonable correlation between a disclosed *in vitro* utility and an *in vivo* activity; a rigorous or exact correlation is not required. However, Applicants respectfully note that the Examiner admits at page 3 of the Office Action that the specification is enabling for the claimed methods *in vitro* while the Examiner has failed to provide any evidence which demonstrates that such *in vitro* examples are not sufficient to enable the *in vivo* activity of the claimed invention.

Applicants also point out that those of skill in the art viewing the specification would know how to formulate the active agents into pharmaceutically acceptable compositions. Applicants point in particular to the specification at page 4 which discloses that the pharmaceutical compositions of the present invention may consist of active agents as well as diluents, carriers and auxiliary agents in addition to other active agents (e.g., cytotoxic agents) which are well known to those skilled in the art. The specification at pages 4 to 5 also provides guidance which is sufficient for the

determination of dosage, for instance the estimation of a dose from cell culture assays, the formulation of dosage in animal models and the estimating of MEC from *in vitro* data. Finally, the specification at page 5 to 6 discloses suitable routes of administration, including injection of the compound directly into a solid tumor.

Therefore, in light of the discussion above, Applicants urge that the claimed invention is sufficiently enabled.

Claim Rejections - 35 U.S.C. § 112, first paragraph

Claims 1, 17 and 19 are rejected as indefinite. Applicants note as a preliminary matter that the Office Action sets forth no reasoning for the rejection of claim 1. Applicants respectfully urge that the rejections of claims 17 and 19 addressed below do not amount to a rejection of claim 1 upon which they are dependent.

The Office Action states that the term "e.g." renders the claim indefinite. Claim 17 has been amended to recite ". . . a disturbed growth factor receptor activation".

The Office Action states that the phrase "pharmaceutically acceptable composition" renders claim 19 indefinite. Claim 19 has been amended to recite a "pharmaceutical composition" which is sufficiently described at page 4 of the specification. The specification at page 4 defines a pharmaceutical composition as a composition wherein the active ingredients are contained in an effective amount to achieve its intended purpose. The specification at page 4 also states that a therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms or a prolongation of survival in a patient. The specification at page 4 furthermore describes determining the toxicity and therapeutic efficacy of such

compounds by standard pharmaceutical procedures in cell cultures or experimental animals.

Claim Rejections - 35 U.S.C. § 102(b)

Claims 1, 4, 5 and 20 are rejected as anticipated by Daub et al. (EMBO J. 16, 7032-7044, 1997). Claim 1 has been amended to indicate that activation of the growth-factor receptor is mediated by its extracellular domain. Applicants note that like all other studies about GPCR-induced transactivation published until the year 2000, Daub et al. discloses an intracellular mechanism. Applicants thus submit that at least the following aspects of the present invention should be acknowledged as novel and inventive. Transactivation is mediated via the extracellular domain of EFGR and thus can be prevented by means of extracellular ligands, for instance blocking antibodies. Critical elements of the transactivation are zinc-dependent metalloproteases and ligands similar to EGF, for example HB-EGF. In addition, the activity of these elements, surprisingly, can be regulated by means of GPCR, these steps being an essential part of the transactivation mechanism. Applicants respectfully urge that the present invention should be considered novel in light of the above amendments and discussion.

Claim Rejections - 35 U.S.C. § 103

Claims 1-16 are rejected as obvious over Daub et al. in view of Dong et al. (Proc. Natl. Acad. Sci. USA 96, 6235-6240, 1999) and in further view of Khandaker et al. (Blood 93, 2173-2185, 1999). The Office Action states that it would have been obvious to study the effects of the metalloprotease inhibitors of Dong et al. in transactivation of

the epidermal growth factor receptor in signaling by GPCR as suggested by Daub et al. and Khandaker et al.

Applicants respectfully submit that none of the cited references, either alone or in combination, teach or suggest the present invention. As discussed above, Daub et al. discloses an intracellular rather than an extracellular mechanism, and accordingly, does not teach or suggest the present invention.

The teachings of Dong et al. refer to autocrine signaling through the EGFR via metalloprotease-mediated EGF-ligand processing. Dong et al. is directed to neither GPCR nor the gene-rating of ligands induced in any other way, by means of regulated proteolytic processing of EGF ligands. The transactivation of EGFR via its extracellular domain is neither taught nor suggested by Dong et al.

Khandaker et al. discloses the LPS or rather TNFα-induced and metalloprotease-mediated processing of GPCR (CXCR1/CXCR2). Khandaker et al. is directed to neither the mitogenic signal transduction of GPCR nor with EGF ligands or EGF receptors. GPCR are the target molecules of the protease and not the regulator. Therefore, like Dong et al. discussed above, the teachings of Khandaker et al. are irrelevant to the present invention.

As evidence of the state of the art at the time of invention, Applicants submit several references which teach that the interaction between GPCR and EGFR is mediated via intracellular signal cross talk, and which were published before the priority date of the present application. In particular, Applicants point to the Abstract of Daub et al. (Nature, **379**: 557-560, 1996), Figure 1 of Luttrell et al. (Current Opinion in Cell Biology, **11**: 177-183, 1999) and Figure 2 of Zwick et al. (*TiPS*, **20**: 408-412, 1999) as

particularly relevant in this regard. However, Applicants note that numerous other publications published before the filing of the present application also hint at such an intracellular mechanism.

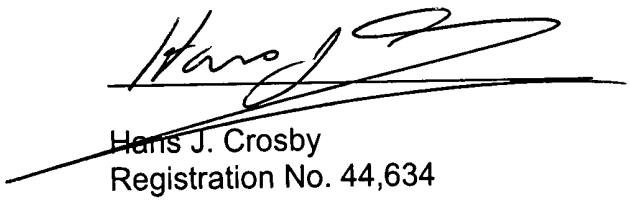
Applicants thus submit not only that the prior art fails to teach or suggest the present invention, in particular that activation is mediated through an extracellular domain, but that such finding was unexpected and surprising in light of the state of the art at the time of invention.

Applicants respectfully urge that in light of the discussion above the claimed invention is in condition for allowance and request early notification to that effect.

In the event this paper is not timely filed, applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, along with any other additional fees which may be required with respect to this paper.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,



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